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Perioperative fluid therapy in neurosurgery

Effects on circulatory and haemostatic variables

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ACADEMIC DISSERTATION

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"We must use the right kind of fluid in appropriate amounts at the right time."

Chappell D et al. 2008

To my husband Mikael,
and daughter Julia.

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles which are referred to in the text by their Roman numerals.

I. Lindroos AC, Niiya T, Randell T, Romani R, Hernesniemi J, Niemi T. Sitting position for removal of pineal region lesions: the Helsinki experience. **World Neurosurgery 2010;74(4/5):503-513.**

II. Lindroos AC, Niiya T, Silvasti-Lundell M, Randell T, Hernesniemi J, Niemi T. Stroke volume-directed administration of hydroxyethyl starch (HES 130/0.4) or Ringer´s acetate in sitting position during craniotomy: a randomised controlled trial. **Acta Anaesthesiol Scand 2013;57(6):729-736.**

III. Lindroos AC, Niiya T, Randell T, Niemi T. Stroke volume-directed administration of hydroxyethyl starch (HES 130/0.4) and Ringer´s acetate in prone position during neurosurgery: a randomised controlled trial. **Journal of Anesthesia; In Press, doi:10.1007/s00540-013-1711-8**

IV. Lindroos AC, Schramko AA, Niiya T, Suojaranta-Ylinen RT, Niemi TT. Effects of combined balanced colloid and crystalloid on rotational thromboelastometry in vitro. **Perfusion 2011; 26(5):422-427.**

V. Lindroos AC, Schramko A, Tanskanen P, Niemi T. Effect of the combination of mannitol and Ringer Acetate or hydroxyethyl starch on whole blood coagulation in vitro. **J Neurosurg Anesthesiol 2010; 22(1): 16-20.**

ABBREVIATIONS

APCO	arterial pressure waveform analysis
BMI	body mass index
CBF	cerebral blood flow
CI	cardiac index
CO	cardiac output
CPP	cerebral perfusion pressure
CT	clotting time
CFT	clot formation time
DD	delta down
DPP	delta pulse pressure
ECG	electrocardiography
$ETCO_2$	end-tidal concentration of carbon dioxide
GDT	goal-directed therapy
HES	hydroxyethyl starch
Hb	haemoglobin concentration
Hct	haematocrit value
HR	heart rate
ICP	intracranial pressure
INR	International Normalized Ratio
LR	lactated Ringer´s
MAC	mimimal alveolar concentration
MAP	mean arterial pressure
MCF	maximum clot firmness
NS	non-significant
$PaCO_2$	arterial carbon dioxide tension
PEEP	positive end-expiratory pressure
Plt	platelet count
PPV	pulse pressure variation

QALYs	quality-adjusted life years
RAC	Ringer´s acetate
ROTEM	rotational thromboelastometry
SAH	subarachnoid haemorrhage
SAP	systolic arterial pressure
SEM	standard error of the mean
SD	standard deviation
SpO_2	arterial saturation of oxygen
SPV	systolic pressure variation
SV	stroke volume
SVI	stroke volume index
SVV	stroke volume variation
TEG	thromboelastography
VAE	venous air embolism

ABSTRACT

Introduction

The major aims with fluid therapy for neurosurgical procedures are to minimize the risk for inadequate cerebral perfusion pressure (CPP) and to maintain good neurosurgical conditions. Excessive fluid restriction to minimize cerebral oedema may lead to haemodynamic instability. Patient positioning, especially sitting and prone positions, may also promote haemodynamic changes due to venous pooling and diminished venous return to the heart. The effect of fluid therapy on coagulation must be considered, because normal coagulation capacity is of particular importance in neurosurgery to prevent bleeding complications.

Patients and methods

This thesis examined the effects of fluid therapy on haemodynamic parameters and coagulation in neurosurgery. The complications of the sitting position were analyzed in a retrospective study. Stroke volume (SV)-directed administration of fluids during neurosurgery in the sitting and the prone position and the effect of a totally balanced fluid concept, and mannitol, on blood coagulation in vitro was examined.

The haemodynamic profile of 72 patients treated for pineal-region tumours in the sitting position were retrospectively evaluated (Study I). Other studies involved 60 adult patients scheduled for elective primary neurosurgery (Studies II and III) and 22 healthy volunteers (Studies IV and V).

Patients were randomized to receive either hydroxyethyl starch (HES) 130/0.4 or Ringer´s acetate (RAC) according to SV-directed administration of fluids, in addition to a basal infusion of 3 mL/kg/h RAC. Before sitting (Study II, n=30) or prone (Study III, n=30) position SV, measured by arterial pressure waveform analysis, was maximized by boluses of study fluid until no increase occurred of more than 10%. SV was maintained by repeated administration of boluses of study fluid during surgery. The volumes of HES and RAC required for stable haemodynamics were compared.

Venous blood collected from 12 healthy volunteers (Study IV) was diluted to 20% and 40% with a combination of an equal amount of colloid (balanced or unbalanced HES 130/0.4 or gelatin) and crystalloid (balanced or unbalanced RAC) in vitro. Venous blood collected from ten healthy volunteers (Study V) was diluted to 10%

and 20% with mannitol alone, mannitol and RAC, and mannitol and HES 130/0.4 in vitro. Blood samples were analyzed with rotational thromboelastometry (ROTEM®).

Results

The sitting position is associated with hypotension and a risk for venous air embolism (VAE) (Study I). We found an intraoperative crystalloid vs. colloid volume ratio of 1.5 (Studies II, III). In Study III, the formation and maximum strength of the fibrin clot were decreased after an average dose of 440 mL of HES 130/0.4. In Study II, an average dose of 460 mL of HES 130/0.4 did not impair the coagulation profile in thromboelastometry. No difference appeared in blood loss between the groups in either study. The combination of balanced colloid and crystalloid had similar coagulation effects in vitro as did their respective combinations of unbalanced solutions (Study IV). We found that mannitol alone and in combination with HES 130/0.4 delayed the initiation of coagulation and fibrin formation and reduced the maximum clot firmness in vitro (Study V).

Conclusions

The sitting position induces hypotension and carries a risk for VAE. SV-directed administration of either crystalloid or colloid stabilizes the haemodynamic parameters in the sitting and prone position. Most of the patients undergoing neurosurgery in either position can be managed with an acceptable volume of RAC. A crystalloid vs. colloid ratio of 1.5 intraoperatively is lower than expected, taking into account the haemodynamic changes induced by the position. The haemodynamic response of goal-directed HES administration was more favourable with regard to cardiac index (CI), and a bolus of HES (<500mL) may be administered when instant restoration of the intravascular volume with minimal fluid loading is indicated. The effect of fluid therapy with HES on coagulation measured in the studies with thromboelastometry varied. The intraoperative blood loss in these patients was very low; the clinical relevance of the findings remains unclear. No advantage with the totally balanced fluid therapy for coagulation emerged. Mannitol alone or in combination with HES 130/0.4 impairs clot propagation and clot strength in vitro.

SAMMANFATTNING

Introduktion

Den främsta målsättningen med vätsketerapi för neurokirurgiska patienter är att minimera risken för otillräckligt blodflöde till hjärnan och samtidigt upprätthålla goda operationsförhållanden för neurokirurgen. Överdriven restriktion av vätsketillförseln för att minimera hjärnsvullnad kan leda till instabil hemodynamik. Placeringen av patienten under operationen, speciellt i sittande eller magläge, kan också förorsaka hemodynamisk instabilitet på grund av ansamling av blod i venerna och minskat tillbakaflöde till hjärtat. Effekten av vätsketerapi på blodets koagulation måste beaktas, emedan normal koagulation är av speciell vikt inom neurokirurgin för att undvika blödningskomplikationer.

Patienter och metoder

I denna avhandling granskas vätsketerapins effekter på hemodynamik samt koagulation inom neurokirurgin. Komplikationerna associerade med sittande läge analyserades retrospektivt. Slagvolym-styrd administration av vätskor under neurokirurgi i sittande och magläge, samt effekten av balanserade vätskor och mannitol på blodets koagulering in vitro undersöktes.

Hemodynamiken hos 72 patienter opererade för tumör i området kring epifysen i sittande läge utvärderades retrospektivt (Studie I). De övriga studierna omfattade 60 vuxna, elektiva neurokirurgiska patienter (Studie II och III) och 22 friska frivilliga (Studie IV och V).

Patienterna randomiserades att få antingen hydroxyetylstärkelse (HES) 130/0.4 eller Ringer´s acetat (RAC) i enlighet med slagvolym-styrd administration av vätskor utöver en infusion av 3 mL/kg/h RAC. Slagvolymen, uppmätt med hjälp av analys av artärkurvan, maximerades före sittande (Studie II, n=30) eller magläge (Studie III, n=30) med hjälp av bolusdoser av vätska tills slagvolymen inte ökade med mer än 10 %. Slagvolymen upprätthölls på denna nivå med hjälp av upprepade bolusdoser av vätska under operationen. Volymerna av HES och RAC som behövdes för en stabil hemodynamik jämfördes.

Venöst blod från tolv friska frivilliga (Studie IV) späddes ut till 20 % och 40 % med en kombination av lika delar kolloid (balanserad eller icke balanserad HES 130/0.4 eller gelatin) och krystalloid (balanserad eller icke

balansed RAC) in vitro. Venöst blod från tio friska frivilliga (Studie V) späddes ut till 10 % och 20 % med mannitol, en kombination av mannitol och RAC, och en kombination av mannitol och HES 130/0.4 in vitro. Blodproverna analyserades med tromboelastometri (ROTEM®).

Resultat

Sittande läge under operationen innebär en risk för hypotension samt venös luftemboli (VAE) (Studie I). I våra studier fann vi ett 1,5:1 förhållande i vätskevolym intraoperativt angående krystalloid jämfört med kolloid (Studier II, III). I Studie III minskade bildandet och den maximala styrkan hos fibrinnätet efter en medeldos av 440 ml med HES 130/0.4. I Studie II försämrade inte en medeldos på 460 ml HES 130/0.4 koagulationen mätt med tromboelastometri. Det förekom inga skillnader i blodförlust mellan grupperna i någondera studien. Kombinationen av balanserad kolloid och krystalloid hade liknande effekter in vitro på koagulationen som respektive kombination av icke balanserade vätskor (Studie IV). Mannitol ensamt och i kombination med HES 130/0.4 fördröjde initieringen av koagulationen och fibrinets bildande samt minskade den maximala styrkan av blodkoaglet in vitro (Studie V).

Konklusioner

Sittande ställning förorsakar hypotension och innebär en risk för venös luftemboli. Slagvolym-styrd administration av antingen krystalloid eller kolloid stabiliserar hemodynamiken i sittande och magläge. De flesta neurokirurgiska patienter som opereras i endera ställningen kan skötas med enbart RAC i moderata volymer. Ett krystalloid vs. kolloid förhållande av 1.5:1 intraoperativt är lägre än förväntat med beaktande av den påverkan patientens ställning har på hemodynamiken. Det hemodynamiska gensvaret av målstyrd HES administration var bättre med tanke på hjärtindex (cardiac index ,CI), och en bolus med HES (<500ml) kan ges när omedelbar återupprättande av intravaskulära volymen med minimal vätskebelastning är indicerad. Effekten av vätsketerapi med HES på koagulationen mätt med hjälp av tromboelastometri varierade. Intraoperativa blodförlusten hos dessa patienter var låg och den kliniska betydelsen av våra fynd förblir oklar. Det framkom inga fördelar med fullständigt balanserad vätskebehandling. Mannitol ensam och i kombination med HES 130/0.4 försämrar koaguleringen in vitro.

YHTEENVETO

Johdanto

Nestehoidon päätavoitteet neurokirurgisen leikkauksen aikana on ylläpitää riittävä aivojen perfuusiopaine ja hyvät leikkausolosuhteet. Liian vähäinen nestehoito, aivoturvotuksen vähentämiseksi, voi johtaa epävakaaseen verenkiertoon. Anestesia erityisesti istuvassa- tai vatsa-asennossa voi heikentää verenkiertoa ja sydämen minuuttivirtausta, koska laskimoveri kerääntyy alaraajoihin ja sen paluu sydämeen heikkenee. Lisäksi nestehoidon mahdolliset vaikutukset veren hyytymiseen tulee huomioida, koska normaali hyytyminen on erityisen tärkeää neurokirurgiassa vuotokomplikaatioiden estämiseksi.

Potilaat ja menetelmät

Tämä väitöskirja selvittää neurokirurgian aikaisen nestehoidon vaikutuksia verenkiertoon ja sydämen toimintaan sekä veren hyytymiseen. Istuvan asennon sivuvaikutuksia tutkittiin aluksi retrospektiivisesti. Sydämen iskutilavuuden ohjaamaa nestehoitoa tutkittiin istuvassa asennossa ja vatsa-asennossa tehtävien neurokirurgisten toimenpiteiden aikana. Täysin balansoitujien liuosten ja mannitolin vaikutuksia veren hyytymiseen selvitettiin kokeellisesti in vitro.

72 istuvassa asennossa, pineaalituumorin takia leikatun potilaan hemodynaaminen profiili analysoitiin retrospektiivisesti (Tutkimus I). Muihin tutkimuksiin rekrytoitiin 60 elektiiviseen neurokirurgiseen toimenpiteeseen tulevaa aikuispotilasta (Tutkimukset II ja III) ja 22 tervettä, vapaaehtoista aikuista (Tutkimukset IV ja V).

Potilaat satunnaistettiin saamaan tausta-infuusiona toimineen Ringerin asetaattiliuoksen (3ml/kg/h) rinnalla iskutilavuuden mukaan ohjattua nestehoitoa, joko HES-liuosta (molekyylipaino 130/0.4) tai Ringerin liuosta (RAC) käyttäen. Ennen siirtymistä istuvaan asentoon (Tutkimus II, n=30) tai vatsa-asentoon (Tutkimus III, n=30) valtimopaineen paineaallon muotoon perustuvan analyysin avulla mitattu iskutilavuus maksimoitiin nesteboluksilla, kunnes se ei enää suurentunut yli 10 % edelliseen mittaukseen verrattuna. Iskutilavuus ylläpidettiin leikkauksenaikaisilla nesteboluksilla ja vakaaseen hemodynamiikkaan tarvittuja määriä HES- ja RAC-liuoksia verrattiin toisiinsa.

12 terveeltä vapaaehtoiselta otettu laskimoverinäyte (Tutkimus IV) laimennettiin in vitro 20 ja 40 prosentin tilavuusvahvuuteen käyttäen yhtä suurista annoksista kolloidia (balansoitu tai ei-balansoitu HES 130/0.4 tai gelatiini) ja kristalloidia (balansoitu tai ei-balansoitu RAC) valmistettua liuosta. 10 terveeltä vapaaehtoiselta otettu laskimoverinäyte (Tutkimus V) laimennettiin in vitro 10 ja 20 prosentin tilavuusvahvuuteen käyttäen pelkkää mannitolia tai mannitolin ja RAC sekoitusta, tai mannitolia ja HES 130/0.4 sekoitusta. Verinäytteet analysoitiin tromboelastometrillä (ROTEM®).

Tulokset

Istuvaan asentoon yleisanestesiassa liittyy hypotension ja laskimoperäisen ilmaembolian riski (VAE). (Tutkimus I). Tutkimuksissamme leikkauksen aikana annetun kristalloidin ja kolloidin välinen tilavuussuhde oli 1,5:1 (Tutkimukset II, III). Tutkimuksessa III fibriiniverkon muodostuminen ja maksimivahvuus väheni keskimääräisesti 440ml HES 130/0.4-annoksen jälkeen. Tutkimuksessa II keskimääräinen annos 460ml HES 130.04 ei häirinnyt tromboelastometrilla mitattua hyytymisprofiilia. Kummassakaan tutkimuksessa ei tullut esiin ryhmien välistä eroa verenhukan suhteen. Balansoiduilla kristalloideilla ja kolloideilla oli in vitro samantapaiset hyytymisvaikutukset kuin vastaavien liuosten balansoimattomilla sekoituksilla (Tutkimus IV). Kokeellisessa tutkimuksessa mannitoli yksinään ja yhdessä HES 130/0.4 kanssa viivästytti hyytymisen ja fibriinin-muodostuksen alkua sekä vähensi hyytymän maksimilujuutta in vitro (Tutkimus V).

Päätelmät

Istuva asento altistaa hypotensiolle ja ilmaembolialle. Sydämen iskutilavuuden ohjaama kristalloidin tai kolloidin anto tasoittaa hemodynaamisia parametreja istuvassa- ja vatsa-asennossa. Suurin osa istuvassa- tai vatsa-asennossa leikattavista neurokirurgisista potilaista voidaan hoitaa hyväksyttävällä määrällä RAC-liuosta. Kristalloidin ja kolloidin leikkauksen aikainen tilavuussuhde oli 1,5:1. Tämä on vähäisempi kuin odotettu, varsinkin kun huomioidaan asennon aiheuttamat hemodynaamiset vaihtelut. Tavoite-ohjattu HES-liuoksen anto oli suotuisaa ajatellen sydämen minuuttivirtausta (cardiac index, CI). HES-bolus (<500ml) voidaan antaa kun välitön suonensisäisen tilavuuden korjaus mahdollisimman pienellä nestemäärällä on aiheellista. Tromboelastometrilla analysoidun, HES-liuoksella toteutetun nestehoidon vaikutus hyytymiseen vaihteli tutkimuksissa. Koska potilaiden leikkauksen jälkeinen verenhukka oli hyvin vähäinen, tämän löydöksen kliininen merkitys jää epäselväksi. Täysin balansoidut liuokset aiheuttivat myös hyytymishäiriön, eikä se eronnut

ei-balansoiduista liuoksista. Mannitoli yksinään tai yhdessä HES 130/0.4 kanssa häiritsee hyytymän muodostumista ja sen vahvuutta in vitro.

INTRODUCTION

Haemodynamic stability and adequate cerebral perfusion pressure (CPP) are of the utmost importance in neuroanaesthesia.[1] Anaesthesia in the sitting and prone position is associated with a significant risk for hypotension [2,3] and decreased cardiac output (CO),[4, 5] which may jeopardize cerebral perfusion, especially if cerebral blood flow (CBF) autoregulation is disturbed. During craniotomy in the sitting position venous pooling of blood into lower extremities,[6] venous air embolism (VAE), [7] or cranial nerve manipulation [8] further aggravates haemodynamic instability.

Fluid management for neurosurgical patients involves several special features and controversies. The patient´s hydration and volume status before the neurosurgery may be affected by emesis, sweating, or fever. Potent diuretics such as mannitol in treatment of intracranial hypertension,[9] intraoperative bleeding, and the possibility of diabetes insipidus[10, 11] may all affect intravascular volume. Patient positioning during surgery also promotes haemodynamic changes.[12,13,14] To preserve adequate cerebral perfusion pressure without causing brain oedema requires preload conditions to be optimal.

Choice of fluid, amount of fluid, and means to monitor the effect of fluid therapy in surgical patients have all been debated for a long time. Several studies have shown the effect of fluid therapy on post-operative outcome.[15] Improved outcome has been demonstrated with goal-directed therapy (GDT) to optimize haemodynamic parameters.[16] Compared with traditional fluid treatment, GDT has also been suggested to lower costs of medical care as well as gain quality-adjusted life years (QALYs).[17]

Movement of water across the intact blood-brain barrier depends primarily on the osmotic gradient between plasma and the brain; osmolarity is therefore a very important property of a solution.[18] Crystalloids (e.g. Ringer´s acetate (RAC) or normal saline) are administered as maintenance fluid intraoperatively, to cover the basal fluid requirements and may be hypo-osmolar, iso-osmolar, or hyperosmolar. Hyperosmolar fluids (e.g. mannitol or hypertonic saline) lower intracranial pressure (ICP).[19, 20] Colloids (albumin, dextran, gelatine, hydroxyethyl starch (HES) solutions) are efficient plasma expanders administered to restore and maintain intravascular volume.[21] The osmolarity of colloids depends on their carrier solutions.

In neurosurgery, normal coagulation capacity is of particular importance to minimize the risk for bleeding complications.[22] Colloids may affect coagulation beyond haemodilution, and HES solutions in particular have been reported to impair coagulation.[23] An HES-induced coagulation disturbance is dose-dependent, [24] and modern, rapidly degradable HES solutions (e.g. HES 130/0.4) have been considered safer.[25, 26] HES 130/0.4 has been used in neurosurgery during brain tumour resection.[27]

The objective of this thesis was to characterize the haemodynamic effects of positioning during goal-directed therapy with a crystalloid or a colloid in neurosurgical patients undergoing surgery in the sitting and prone positions, and to assess the effect of the fluids used in neurosurgical patients on coagulation.

REVIEW OF THE LITERATURE

PATIENT POSITIONING IN NEUROSURGERY

The sitting position (Figure 1) provides optimal access to intracranial posterior midline lesions and has served for posterior fossa, as well as cervical spine surgery.[4] Because of its potential for serious complications, use in cervical spine surgery has, however, declined; neurosurgical centres using the sitting position for posterior fossa surgery are also diminishing.[4] Although this position does improve cerebral venous drainage, lower intracranial pressure, and promote gravity drainage of blood and cerebral spinal fluid from the surgical field, [4] possible complications related to the sitting position include haemodynamic instability, VAE, pneumocephalus, quadriplegia, and compressive peripheral neuropathy.[4] General anaesthesia in the sitting position is associated with hypotension; CO can decrease by 10 to 20%.[4] Possible mechanisms are venous pooling in the lower extremities and redistribution of blood volume from the intra- to the extrathoracic compartment.[2] VAE can occur in any position with a negative pressure gradient between the surgical site and the right atrium, and VAE has occurred although not so frequently during neurosurgery in the lateral, supine, or prone positions as well. [28,29]

Figure 1. Sitting position. From the book by M Lehecka, A Laakso, J Hernesniemi. *Helsinki Microneurosurgery Basics and Tricks*, 2011. Printed with the kind permission of the authors.

The prone position (Figure 2) provides surgical access to the posterior head, neck, and spinal column and is used for spinal surgery as well as parietal, occipital, and suboccipital craniotomies.[28] General anaesthesia in the prone position is associated with hypotension,[30] and CO has been reported to decrease 17 to 24%.[5] Possible mechanisms behind the CO reduction are reduced venous return, direct effects on arterial filling, and reduced left ventricular compliance secondary to increased thoracic pressure.[5] Abdominal compression causing obstruction of the inferior vena cava reduces CO further and also promotes blood loss during spinal surgery due to increased filling of the vertebral column veins.[5] Further complications associated with neurosurgery in the prone position are cervical spine injury, spinal cord ischaemia, pneumocephalus, peripheral nerve injury, postoperative visual loss, and VAE.[5]

Figure 2. Prone position. From the book by M Lehecka, A Laakso, J Hernesniemi. *Helsinki Microneurosurgery Basics and Tricks*, 2011. Printed with the kind permission of the authors.

PERIOPERATIVE FLUID MANAGEMENT

Perioperative fluid therapy is part of almost all surgical procedures, and although an everyday issue is still controversial. This practice has varied from `liberal´ to `restrictive´. The principles of a restricted fluid regimen were introduced as early as in the late 1950s by Francis Moore. In the 1960s Tom Shires came up with the concept of `third space losses´ due to redistribution of fluids during surgery; he also postulated replacement of these losses.[31] Later, the existence of this `third space´ has been questioned,[32] and excess fluid replacement is suggested to accumulate interstitially.[33] With no established definition of `liberal´ and `restrictive´ fluid therapy and inconsistent study designs, a comparison of the two different fluid regimen is difficult.[15] Most of the studies regarding `restrictive´ fluid therapy include only abdominal surgery with high-risk patients excluded, and the results can therefore not be directly applied to all surgical patients.[15]

Normovolaemia is a widely accepted goal for fluid therapy in neurosurgical patients, although perioperative fluid therapy in these patients has been scarcely investigated. Stroke volume variation (SVV) as well as delta pulse pressure (DPP) and delta down (DD), derived from the variation in arterial pressure associated with mechanical ventilation, has predicted fluid responsiveness accurately in neurosurgical patients.[34, 35] According to a study in subaracnoid haemorrhage patients (SAH), comparing APCO with a pulmonary artery catheter, the second generation of the FloTrac®/Vigileo® monitoring system underestimates CO values.[36] In another study comparing uncalibrated APCO to transpulmonary thermodilution (PiCCO) for GDT after SAH, the third-generation FloTrac®/Vigileo® still underestimates CI during hyperdynamic therapy with dobutamine, but it may be acceptable to measure trends of CI.[37] In patients undergoing elective brain surgery, however, SVV obtained by the third-generation FloTrac®/Vigileo® is a sensitive predictor of fluid responsiveness.[38]

The stress induced by surgery causes release of stress hormones reducing the excretion of salt and water during surgery.[39] Anaesthetics per se are not associated with extravascular retention of fluids in surgical patients, but anaesthesia-related hypotension affects the kinetic behaviour of fluids.[40] In the absence of surgical stress, isoflurane anaesthesia in volunteers altered the disposition of fluids, because of reduced clearance and a slower distribution, with approximately 10% more of the fluid bolus accumulated in the peripheral compartment.[41] Fluid loading has minimal influence on anaesthesia-related hypotension,[41] and this should preferably be treated with vasopressor therapy.[42] Serum colloid osmotic pressure falls in response to surgery,[43] and this affects

intravascular volume. After major surgery, endothelial glycocalix changes occurs similar to those in sepsis, but to a lesser extent; this may cause a non-specific capillary leak syndrome.[44]

The aim of perioperative fluid therapy is to maintain the circulating plasma volume and thus ensure organ perfusion and oxygen delivery to the tissues.[45] This has traditionally been achieved by infusion of large volumes of fluids,[45] resulting in a positive intraoperative fluid balance, which can, however, be associated with significant morbidity postoperatively.[46] Generally fluid therapy includes replacement of basal fluid requirements and fluid losses such as by perspiration, blood loss, and exudation through the surgical wound; as well as maintenance of physiological functions to avoid hypotension.[39]

Perioperative hypovolemia induces hypotension and may cause organ dysfunction, increased post-operative morbidity, and death.[47] Excess fluid replacement, on the other hand, leads to increased demands on cardiac and kidney function and may cause pulmonary, intestinal, and subcutaneous oedema with impaired oxygen diffusion to the tissues.[48] GDT in the perioperative period reduces surgical complications and also improves long-term survival. [16, 49,50] Perioperative GDT reduces surgical site infections, pneumonia, and urinary tract infections, [51] as well as gastrointestinal complications.[52] Compared to conventional fluid therapy, perioperative GDT also reduces the incidence of acute kidney injury,[53] mainly by minimizing the harmful effects of fluid overload.[54] Not all studies of GDT report positive results, however; one study of GDT in open elective abdominal aortic surgery reports no effect on the incidence of post-operative complications,[55] and GDT for vascular surgery patients did not result in higher tissue oxygen delivery.[56] Tissue perfusion monitoring remains controversial; the ideal marker of tissue perfusion is still lacking.[50] Concern has arisen that most of the studies about GDT are single-centre trials and underpowered to detect a difference in mortality.[57]

The concept of fluid resuscitation aiming for supra-normal haemodynamic parameters was introduced by Shoemaker in the 1970s and 1980s.[58] At the start, GDT required use of the invasive technique of a pulmonary artery catheter for haemodynamic monitoring.[59] Minimally invasive haemodynamic monitoring including oesophageal Doppler and APCO such as by SVV and pulse pressure variation (PPV) have been developed in recent years. According to one systematic review, both morbidity and mortality were reduced with use of the newer generation of monitoring as well as with the pulmonary artery catheter for pre-emptive haemodynamic

monitoring.[16] In a meta-analysis, all forms of haemodynamic monitoring for GDT appeared to be equally effective in reducing perioperative complications.[60]

Individualized GDT is based on the physiological principle of the Frank-Starling law of the heart, with a curvilinear relationship between ventricular preload and ventricular stroke volume (Figure 3).[61] An increase in preload induced by volume expansion will increase stroke volume until the plateau phase.[62] The Frank-Starling relationship also depends on ventricular function, and the curve is flattened when ventricular function is impaired.[62] Mechanical ventilation induces cyclic changes in vena cava blood flow, pulmonary artery blood flow, and aortic blood flow.[63] As a consequence, mechanically ventilated patients present with cyclic changes in left ventricular stroke volume.[64] These respiratory variations are related to the patient´s fluid status, and in hypovolemic patients, the systolic pressure variation (SPV) is frequently over 10 mmHg.[65] SPV is an accurate predictor of fluid responsiveness in adult patients undergoing noncardiac surgery.[66] The dynamic indices SPV, PPV, and SVV predict fluid responsiveness in mechanically ventilated patients accurately.[67]

SVV correlates well with SPV in cardiac surgery patients.[68] In response to a 500 mL fluid challenge in coronary artery bypass grafting patients, SVV of more than 10% predicted a 15% increase in CO at a sensitivity of 82% and a specificity of 87%.[69] Dynamic parameters of fluid responsiveness such as SPV, SVV, and PPV have several limitations. These parameters must be used in fully sedated, mechanically ventilated patients, with a tidal volume of at least 8 mL/kg of body weight, sinus rhythm, and an intra-abdominal pressure within normal ranges.[62] Furthermore, accuracy of APCO may be limited during rapid changes in vascular resistance, for example during pharmacologically induced vasoconstriction.[70]

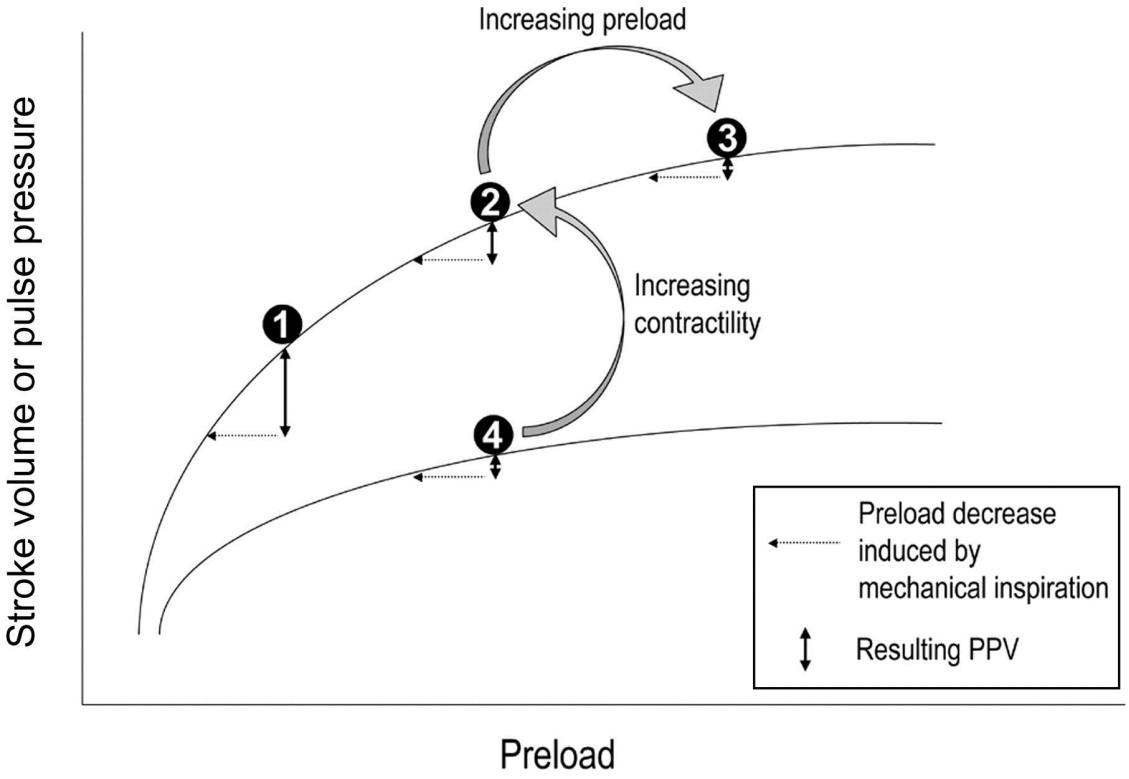


Figure 3. The Frank-Starling curve. Increasing preload induces a decrease in PPV (from 2 to 3). PPV is minimal when the heart is operating on the plateau of the curve (3 and 4). Decreasing preload induces an increase in PPV (from 2 to 1), also increasing contractility (from 4 to 2). © Biomed Central. Michard and colleagues. *Crit Care* 2007;**11**:131, doi:10.1186/cc5905. Permission to reproduce granted under BioMed Central´s general terms.

INTRAVENOUS FLUIDS IN NEUROSURGERY

CRYSTALLOID SOLUTIONS

Crystalloids contain no high-molecular-weight compounds and thus have an oncotic pressure of zero. Isotonic crystalloids distribute evenly across the whole extracellular compartment, only 20% remaining in the vascular compartment.[32] According to a study in surgical patients, the intravascular volume effect of lactated Ringer´s (LR) solution is 17 ±10%.[71]

Crystalloids may be hypo-osmolar, iso-osmolar, or hyperosmolar. In healthy volunteers receiving 50 mL/kg LR solution (273 mOsm/L) and 0.9% saline (308 mOsm/L), LR transiently reduced serum osmolality, whereas

normal saline failed to change serum osmolality but caused metabolic acidosis.[72] Saline-based fluids are associated with risk for hyperchloraemic metabolic asidosis.[73] Ringer´s solutions are buffered with either lactate or acetate. The composition of ions in RAC is very close to that of the extracellular fluid, but RAC (270 mOsm/l) is slightly hypo-osmolaric in relation to plasma (295 mOsm/l); therefore additional sodium may be needed. Serum osmolality affects brain water content, so that low serum osmolality may contribute to cerebral oedema.[74] Hypo-osmolar solutions should be avoided in neurosurgical patients.[75]

Moderate haemodilution with crystalloids in patients undergoing peripheral vascular surgery under regional anaesthesia induces an enhanced coagulation state as measured by thromboelastograph (TEG) analysis and in routine coagulation studies.[76] The mechanism is related to rapid haemodilution; possibly to a reduction in anticoagulant factors such as antithrombin III.[76] This hypercoagulability continues into the postoperative period [77] and is also suggested to elevate the incidence of deep vein thrombosis.[78]

Extracellular losses, such as urinary output and perspiration, should be replaced with isotonic crystalloids.[32] Optimal perioperative fluid therapy is suggested to include a combination of fixed crystalloid to replace extravascular losses and avoidance of fluid excess, together with individualized goal-directed colloid administration to maintain maximal stroke volume.[15] The clinical studies of GDT all include administration of colloids, [79] and GDT-administered crystalloid has only been studied in animal models.[80, 81]

COLLOID SOLUTIONS

Albumin, dextran, gelatin, and HES solutions are efficient plasma expanders widely used in the replacement of fluid volume for surgical patients. The duration of the volume effect of colloids varies according to their molecular weight. Gelatins and albumin are more likely to leak into the interstitial space, whereas HES solutions are retained in the blood circulation longer.[82] The osmolarity of colloids is dependent upon the carrier solution; for example, 6% tetrastarch (HES 130/0.4) is dissolved in normal saline (308 mOsm/l). According to one systematic review no evidence exists that any one particular colloid is safer or more effective.[83] A previous systematic review has also suggested that colloids are no more effective than crystalloids in reducing mortality during fluid resuscitation in patients with trauma, or burns, or following surgery.[84]

Safety is a concern with regard to coagulopathy, renal failure, and mortality associated with HES solutions, and although HES solutions with a lower molecular weight and degree of substitution such as HES 130/0.4 are considered safer, evidence may be insufficient to support this.[85] The impact of the raw material of HES solutions (potato-derived versus waxy maize-derived) has been discovered in recent years, and waxy maize-derived 6% HES 130/0.4 may have advantages.[86] In healthy volunteers, the pharmacokinetic properties of the waxy maize-derived and potato-derived solutions differed, [87] and a recent experimental study also suggests differing biological effects of these two starch types.[88]

The effects of HES solutions on blood coagulation both in vitro and in vivo that observed with TEG increase in a dose-dependent manner, including a decrease in the rapidity of clot formation and clot strength.[89] Compared to other HES solutions, HES 130/0.4 has the smallest effect.[89] No disturbance of haemostasis occurred in neurosurgical patients receiving 1000 mL of 6% HES (Plasmasteril®), although HES prevented the postoperative increase in factor VIII activity that otherwise would contribute to postoperative hypercoagulability.[90]

Recently two large studies (6S trial and CHEST study) comparing HES 130/0.4 to a crystalloid for fluid resuscitation in patients with severe sepsis have reported an increased risk for acute kidney injury or need for renal replacement therapy with HES 130/0.4.[91, 92] Results regarding patient survival differed between these two studies, with no difference in 90-day mortality between groups in the CHEST study.[92] In the CRYSTAL study, which investigated mortality in ICU patients treated with any available crystalloid compared to any available colloid, colloid resuscitation reduced 90-day mortality in patients suffering from sepsis or nonseptic shock, but not in trauma patients. (Djillali Annane, FRACTA meeting 2013). Conflicting results concerning use of modern starch solutions in septic patients may at least partly be due to differences in transfusion protocols, with early or late fluid resuscitation, and to nonprotocolized or protocolized infusion of fluids. The CRYSTMAS study with early goal-directed therapy in hypovolemic patients with severe sepsis showed no differences in adverse events between patients treated with HES 130/0.4 or with isotonic saline.[93] The consensus statement of the ESICM task force on colloid volume therapy in critically ill patients suggests avoidance of 6% HES 130/0.4 or gelatin in patients with severe sepsis or risk for acute kidney injury, and recommend no use of colloids in patients with head injury.[94] This recommendation of no colloids for head injury is under debate with the suggestion that albumin and gelatin may increase risk for brain oedema through low osmolarity, irrespective of the colloid

preparation itself.[95] The concern is that in patients with an impaired blood-brain barrier, HES solutions may penetrate into the brain interstitium, despite the absence of HES in cerebrospinal fluid.[96] On the other hand, a reduction in colloid oncotic pressure can aggravate traumatic brain oedema.[97]

In surgical patients without an elevated risk for acute kidney injury, colloid use is still an open question. In one recent review were no indications that tetrastarches (HES solutions with molar substitution ratio 0.4 or 0.42) used intraoperatively or in the immediate postoperative period induce adverse renal effects, increased blood loss, or increased mortality.[98] Most studies in the perioperative setting have a small sample size and a short follow-up time, however, and are unsuitable for conclusions as to HES-solution safety. Approaching the question of colloid safety physiologically, focusing on mechanisms behind the acute kidney injury, an experimental study found that normovolemic haemodilution with crystalloids but not starches (HES 6% 130/0.4) reduced microcirculation in the kidney.[99]

A common belief that intravascular volume replacement with crystalloid solutions requires three times as much fluid or even more than for colloids.[100] According to recent studies in critically ill patients, the crystalloid-to-colloid-volume ratio is in fact more in the range of 1 to 2.[101] In the perioperative setting, crystalloid-to-colloid volume ratios have not been systematically assessed. With progressive normovolaemic haemodilution, as in the case of acute bleeding, the requirement of crystalloid to blood loss is, however, fivefold, and colloids may prevent interstitial fluid accumulation.[71] There is an indication for colloids in the replacement of plasma deficits due to acute blood loss or protein-rich fluid shifts toward the interstitial space.[32]

HYPEROSMOLAR SOLUTIONS

Hyperosmotic fluids are useful in fluid resuscitation not only for patients with haemorrhagic hypovolemia but also for patients with intracranial hypertension. Hyperosmolar therapy with either mannitol or hypertonic saline reduces ICP by reducing brain volume.[19] Mannitol induces osmotic diuresis, whereas hypertonic saline increases serum osmolarity directly.[19] Mannitol is administered to improve surgical conditions during craniotomy, but rebound increase in intracranial pressure has been a concern; [102] after high doses of mannitol, one complication is acute kidney injury.[103] Renal insufficiency is usually transient and completely reversible.[104] With hypertonic

saline, possible concerns are the sodium load and hypernatremia.[75] The patient´s haemodynamic status and renal function influence the choice of osmotic agent.[19]

BALANCED FLUIDS

LR and more recently developed balanced solutions are buffered and have electrolyte compositions close to that of plasma. Traditionally, HES is dissolved in isotonic saline, but solutions now developed contain HES dissolved in balanced electrolyte solutions. Infusion of large volumes of saline results in hyperchloraemic metabolic acidosis.[105] The clinical relevance of the hyperchloraemic metabolic acidosis is debatable, but it has been associated with increased need for blood products[106] as well as renal cortical tissue perfusion reduction.[107] According to one retrospective cohort trial in noncardiac surgical patients, the incidence of acute postoperative hyperchloremia was 22%.[108] The hyperchloremia was associated with increased risk of 30-day mortality.[108] Administration of completely balanced fluids (crystalloid and colloid) to surgical patients also has resulted in better gastric mucosal perfusion than with saline-based solutions.[109] In a retrospective cohort study regarding replacement of fluid losses on the day of surgery, compared to normal saline balanced crystalloid was associated with less postoperative morbidity.[110]

Important for optimal coagulation capacity is acid-base- and electrolyte homeostasis.[111] Balanced solutions are hypothesized to interfere less with coagulation, but according to one study in volunteers receiving 20 mL/kg balanced (Vitafusal®) or saline-based (Venofundin®) tetrastarch 6% 130/0.42, the effect of the carrier solution on platelet aggregation and clot formation assessed by blood aggregometry and rotational thromboelastometry was minimal.[112] In surgical patients, however, 6% hetastarch in a balanced-saline vehicle (Hextend®), as determined by thromboelastography, was associated with minimal effect on haemostasis, compared to that of 6% hetastarch in normal saline (Hespan®) that induced hypocoagulation. [77]

PERIOPERATIVE COAGULATION MANAGEMENT

For patients undergoing any surgery, perioperative monitoring of coagulation aims for increased safety.[113] In neurosurgical patients, abnormal haemostasis leading to bleeding complications can cause severe impairment, or even death.[114] In guiding coagulation management perioperatively, routine coagulation tests (prothrombin time,

International Normalized Ratio (INR), activated partial thromboplastin time, fibrinogen) have limitations, such as delayed test results, insufficient differential diagnosis of acquired intra-operative coagulopathy, and insensitivity to the function of fibrinogen, hyperfibrinolysis, and platelet dysfunction.[113] Perioperative visco-elastic point-of-care testing enables early detection of the underlying coagulopathy.[114] The advantage of these techniques is that they measure the entire clotting process bedside, with minimal delay.[115]

Since thromboelastography was first described in 1948 by Hartert, the visco-elastic whole blood testing of today has developed thromboelastography (TEG®), thromboelastometry (ROTEM®), and the Sonoclot® analyzer.[116] These all measure shear-elastic features during clot formation in recalcified citrated or noncitrated blood and provide graphical representations as well as numerical data for such parameters as time to clot, rate of formation of the clot, strength of the clot, and stability of the clot, along with assessment of fibrinolysis.[116] ROTEM® improved the original TEG® procedure and implemented test modifications to facilitate differential diagnosis, such as fibrinogen deficiency, thrombocytopenia, prolonged clot generation due to various coagulation-factor deficiencies, or to heparin, and impaired clot stability due to hyperfibrinolysis and factor XIII deficiency.[113]

A normal ROTEM® tracing is in Figure 4. EXTEM uses recombinant tissue factor to activate coagulation and assess coagulation through the extrinsic pathway.[113] In the FIBTEM test, cytochalsin D, a platelet inhibitor, allows assessment of the contribution of fibrinogen to clot strength.[113] Comparing FIBTEM and EXTEM results permits differentiation of a low platelet count from dys- or hypofibrinogenaemia.[113] In the APTEM test, aprotinin inhibits fibrinolysis, and the degree of fibrinolysis is assessed by comparison of EXTEM and APTEM results.[113] INTEM uses ellagic acid contact activator to analyze general coagulation status through the intrinsic pathway.[113] HEPTEM can serve to detect specific anticoagulant effects.[113]

Criticism has araisen against viscoelastic point-of-care coagulation monitoring because these tests are hard to standardize.[115] Concern arises about quality control, but according to a recent study, the reproducibility of ROTEM® was not influenced by its performance bedside or, alternatively, in the hospital laboratory.[117] Influences on the parameters determined by ROTEM® are age, gender, and oral contraception; adjustments for these factors may be necessary when ROTEM® is used to screen for distinct abnormalities of haemostasis.[118]

In neurosurgical patients, TEG® revealed increased coagulability during surgery, changes more pronounced in patients undergoing craniotomy than in patients undergoing spinal procedures.[119] Thromboplastin, an activator of the extrinsic pathway of the coagulation cascade, is released during intracranial surgery and may contribute to the hypercoagulability.[120]

According to one systematic review, use of TEG® or ROTEM® in patients with massive transfusion reduced bleeding and reduced the proportion of patients requiring transfusion of both platelets and fresh frozen plasma, although with no effect on patient survival.[121] In surgical patients, point-of-care-guided coagulation management reduces patient exposure to allogeneic blood products and provides a better clinical outcome.[122]

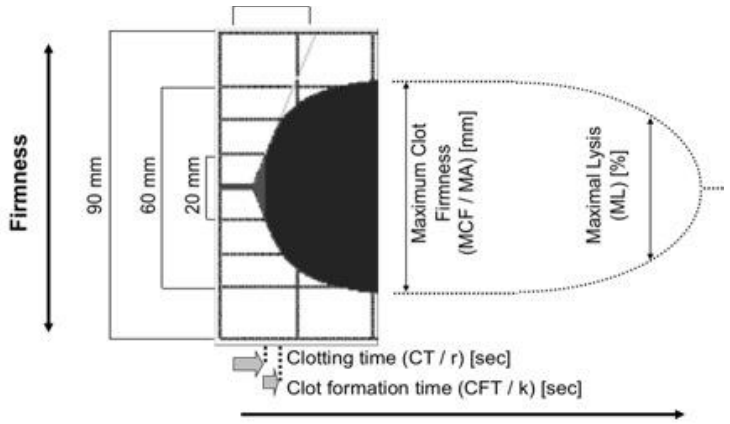


Figure 4. Normal thromboelastometry (ROTEM®) tracing and parameters. From "A Practical Guide to Laboratory Haemostasis", Practical-Haemostasis.com. Printed with permission from the website owner.

AIMS OF THE STUDY

The main objective of the study was to examine the circulatory and coagulation variables during goal-directed fluid therapy with a crystalloid or a colloid in patients undergoing neurosurgery in the prone or sitting position.

The specific aims were to determine:

1. the haemodynamic profile and the incidence of venous air embolism (VAE) in patients undergoing surgery in the sitting position (I, II).
2. the volumes of HES 130/0.4 and Ringer´s acetate required for stable haemodynamics during neurosurgery in the sitting position by use of stroke volume-directed administration of fluids (II).
3. the volumes of HES 130/0.4 and Ringer´s acetate required for stable haemodynamics during neurosurgery in the prone position by use of stroke volume-directed administration of fluids (III).
4. the effect of a totally balanced fluid concept on whole blood coagulation in vitro (IV).
5. the effect of mannitol with or without HES on whole blood coagulation in vitro (V).

PATIENTS AND METHODS

This study was carried out at Töölö Hospital, Helsinki University Central Hospital, Helsinki, Finland, during 2008 to 2012. Altogether 60 neurosurgical patients (Studies II, III) and 22 volunteers (Studies IV, V) were recruited for the study (Table 1). In addition, the anaesthesiology reports of 72 neurosurgical patients were reviewed retrospectively (Study I). All the studies were approved by the ethics committee of the hospital district, and Studies II and III were also approved by the National Agency of Medicines in Finland. All patients and volunteers gave their written informed consent. Characteristics of the study fluids are in Table 2.

Table 1. Study characteristics.

Study	Subjects	n	Design	Intervention	Primary end-point
I	Neurosurgical patients: sitting	72	Retrospective	None	Haemodynamic stability and incidence of VAE
II	Neurosurgical patients: sitting	30	Prospective, randomized, open, controlled	SV-directed administration of HES 130/0.4 or RAC	Volumes of HES and RAC
III	Neurosurgical patients: prone	30	Prospective, randomized, open, controlled	SV-directed administration of HES 130/0.4 or RAC	Volumes of HES and RAC
IV	Healthy volunteers	12	Experimental in vitro, randomized, cross-over	20 and 40 vol% haemodilution with a combination of balanced or unbalanced colloid (HES 130/0.4 or 4% gelatin) and balanced or unbalanced RAC	ROTEM ® parameters (MCF)
V	Healthy volunteers	10	Experimental in vitro, randomized, cross-over	10 and 20 vol% haemodilution with 15% mannitol, mannitol and RAC, and mannitol and HES 130/0.4	ROTEM ® parameters (MCF)

HES= hydroxyethyl starch, MCF= maximum clot firmness, RAC= Ringer´s acetate, ROTEM= rotational thromboelastometry, SV= stoke volume, VAE= venous air embolism

Table 2. Characteristics of the study solutions

	RAC	Balanced RAC	6% HES 130/0.4	6% Balanced HES 130/0.4	4% GEL	15% Mannitol
Study	II,III,IV,V	IV	II, III,IV,V	IV	IV	V
Average MW, kDa	-	-	130	130	30	182
pH	6.0	4.6-5.4	4.0-5.5	5.7-6.5	7.1-7.7	4.5-7.0
Sodium, $mmolL^{-1}$	131	140	154	137	154	-
Chloride, $mmolL^{-1}$	112	127	154	110	120	-
Potassium, $mmolL^{-1}$	4	4	-	4	-	-
Calcium, $mmolL^{-1}$	2	2.5	-	-	-	-
Magnesium, $mmolL^{-1}$	1	1	-	1.5	-	-
Acetate, $mmolL^{-1}$	30	24	-	34	-	-
Malate, $mmolL^{-1}$	-	5	-	-	-	-
Osmolarity, $mOsmL^{-1}$	270	309	308	286.5	274	825

GEL=gelatin, HES= hydroxyethyl starch, MW=molecular weight, RAC= Ringer´s acetate

RETROSPECTIVE STUDY (I)

In Study I, anaesthesiology reports of 72 patients, aged 1-78, treated for pineal region tumours in the sitting position in 1997-2007 were reviewed for haemodynamic stability and incidence of VAE. VAE was defined as an embolic heart sound by precordial Doppler ultrasound, a 0.7 kPa or greater decrease in end-tidal concentration of carbon dioxide ($ETCO_2$), or identification of an air leak at the surgical site.

PROSPECTIVE CLINICAL STUDIES (II, III)

Patients

Thirty adult neurosurgical patients undergoing surgery in the sitting position (Study II) and thirty adult neurosurgical patients undergoing surgery in the prone position (Study III) were randomized to receive either HES 130/0.4 or RAC according to SV-directed administration of fluids. Exclusions were age <18, body mass index (BMI) >36 ($kg \cdot m^{-2}$) (Study III) or >40 ($kg \cdot m^{-2}$) (Study II), congestive heart failure, other than sinus rhythm, renal failure (P-creatinine>120 $micromol \cdot L^{-1}$), hepatic failure, anaemia (haemoglobin concentration, Hb

<100 $g \cdot L^{-1}$), thrombocytopenia (platelet count, Plt <100 $\cdot 10^9$ L^{-1}), and anticipated need for mannitol during the surgery. Also observed were general contraindications for the sitting position such as known open foramen ovale, ventriculoatrial shunt, uncontrolled hypertension, cerebral ischaemia when upright and awake, right atrial pressure greater then left atrial pressure, and age >80 years (Study II).

Anaesthesia

Patients fasted for at least 6 hours preoperatively. Preoperative cardiac medication was administered on the morning of surgery, except for angiotensin-converting enzyme inhibitors and angiotensin II antagonists. Oral diazepam 5-20 mg served for premedication. All patients received a basal infusion of RAC started at a rate of 3 $mL \cdot kg^{-1}h^{-1}$ before induction of anaesthesia. Preoperative antibiotics (cefuroxime or vancomycin) were administered to all. Anaesthesia was induced in the supine position with fentanyl 2-7 $microg \cdot kg^{-1}$ and either thiopenthal 2-7 $mg \cdot kg^{-1}$ or propofol 2-3 $mg \cdot kg^{-1}$. All patients were given glycopyrrolate 0.2 mg and rocuronium (0.5-0.9 $mg \cdot kg^{-1}$) for muscle relaxation. Anaesthesia was maintained with sevoflurane (1 minimal alveolar concentration, MAC) in a mixture of nitrous oxygen and air (Study III), or a continuous infusion of propofol (4-12 $mg \cdot kg^{-1} \cdot h^1$) and remifentanil (0.05-0.45 $microg \cdot kg^{-1} \cdot h^1$) (Studies II and III). The patients were tracheally intubated and mechanically ventilated with volume-controlled ventilation for a tidal volume of 8 to10 $mL \cdot kg^{-1}$ body weight at a rate of 10-15 min^{-1} for normoventilation (target arterial carbon dioxide tension, $PaCO_2$ 4.5 to 5.0 kPa) without positive end-expiratory pressure (PEEP). Ventilatory settings were constant during data recording.

Monitoring

Our routine monitoring consisted of non-invasive arterial pressure, electrocardiography (ECG) (lead II), arterial saturation of oxygen (SpO_2), and after intubation and the start of mechanical ventilation, nasopharyngeal temperature, side-stream spirometry (Side stream®, Datex-Ohmeda Inc, GE Healthcare, Madison, WI, USA), and $ETCO_2$. Invasive monitoring of arterial pressures and blood samples was obtained through a 20-G arterial catheter (Becton Dickinson, Temse, Belgium) inserted into the radial artery after the induction of anaesthesia. A pressure transducer (FloTrac®, Edwards Lifesciences, Irvine, CA, USA) was connected to the radial arterial line and to the Vigileo® System (Edwards Lifesciences) with software v 3.02. This device enables continuous monitoring of CO by pulse contour analysis without external calibration. The system provides CO, CI, SV, SVI, and SVV. Invasive arterial blood pressure was measured at the level of the heart (Study III) or at the level of

foramen Monro (Study II) through a second blood pressure transducer set connected to the radial arterial line. Target mean arterial pressure (MAP) was 60 mmHg or higher, and if MAP was below 60 mmHg, boluses of phenylephrine (0.05-0.1 mg) or ephedrine (5-10 mg) were provided. If MAP remained below 60 mmHg for longer than 5 min, a phenylephrine-infusion was started. In the sitting position (Study II) the probe of precordial Doppler (Versatone D8 Perioperative Doppler; MedSonics Inc, Mountain View, CA, USA) was attached to the right of the sternum over the fifth intercostal space.

Fluid boluses

In the supine position after induction of anaesthesia, an initial 200 mL bolus of the study fluid was infused over 2 to 4 minutes, and haemodynamic measurements were performed before and 3 min after the volume expansion. Thereafter, 100-mL boluses were infused over 2 to 4 minutes. Haemodynamic measurements were performed at 3 min after the completion of each bolus, and a new bolus was given immediately after the measurements, until the SV increase was no more than 10%. In the sitting (Study II) or prone (Study III) position, measurements during surgery were performed at 5-min intervals. If SV decreased more than 10% from the value obtained in the supine position, further boluses of 100 mL of the study fluid were infused. If the SV did not increase with three consecutive boluses of study fluid during surgery, volume expansion was stopped, and the patient was considered a non-responder. Finally, haemodynamic measurements were performed at the end of surgery, and in the supine position. Postoperatively, the basal infusion of RAC was given at a rate of 1 $mL \cdot kg^{-1}h^{-1}$ to all patients until the following morning.

Type of surgery

In Study II, all patients underwent elective craniotomy. Study III included several types of elective neurosurgery: spinal surgery at the cervical, thoracic or lumbar site, Chiari surgery (decompression of posterior fossa) and craniotomy.

IN VITRO STUDIES (IV, V)

In Study IV, venous blood collected from six healthy male and six healthy female volunteers aged 19 to 28 was diluted to 20% and 40% end-concentrations with a combination of equal amounts of colloid (balanced or unbalanced HES 130/0.4 or gelatin) and crystalloid (balanced or unbalanced RAC) in vitro. In Study V, venous

blood samples from seven healthy male and three healthy female volunteers aged 22 to 44 were diluted to 10% and 20% end-concentrations with mannitol (15% Mannitol) alone, mannitol and RAC, and mannitol and HES 130/0.4 in vitro. None of the volunteers was on regular medication, and any drug affecting haemostasis was forbidden for at least 5 days before blood sampling. Hb, haematocrit value (Hct), and Plt were determined in whole blood and in the diluted samples. All blood samples were analyzed with modified thromboelastometry (ROTEM®; Pentapharm Co., Munich, Germany).

SAMPLE HANDLING

In the clinical studies (II and III), arterial blood samples were collected after the induction of anaesthesia (Pre), after the total amount of boluses of the study infusion given in the supine position before positioning (Post), and at the end of surgery (End) via a non-heparinized radial artery catheter. Blood samples were collected into polypropylene tubes containing 3.2% buffered citrate. In the in vitro studies (IV and V), each venous blood sample was obtained from an antecubital vein directly into a vacuum polypropylene tube containing 3.2% buffered citrate. Immediately after sampling, part of the whole blood was diluted with the test solutions in random order. An undiluted citrated blood sample served as a control.

For Studies II to V, modified thromboelastometry coagulation analysis (ROTEM®; Pentapharm GmbH, Munich, Germany) was performed within 2 hours after blood withdrawal. Studies IV and V used extrinsic ROTEM (tissue coagulation activator, EXTEM®) and fibrinogen ROTEM (FIBTEM®), and Studies II and III had an additional two tests performed: intrinsic ROTEM (contact coagulation activator, INTEM®) and aprotinin ROTEM (APTEM®)). Coagulation was allowed to proceed for at least 30 minutes. Automatically measured ROTEM® variables were clotting time (CT,s), clot formation time (CFT,s), α-angle (degree), and maximum clot firmness (MCF, mm).

In Studies II and III blood samples were analysed for Hb, Hct, and Plt with the Sysmex K-4500® (Sysmex Corporation, Kobe, Hyogo, Japan). In Study IV, blood samples were analysed for Hb, Hct, and Plt with the Sysmex KX-21N haematology analyser® (Sysmex America, Mundelein, IL, USA). Study V blood samples were analysed for Hb, Hct, and Plt with the Cell-Dyn 610 Haematology Analyser® (Sequoia-Turner Corporation,

Mountain View, CA, USA). Arterial blood gases were analysed in Studies II and III with the Radiometer ABL825® (Radiometer, Copenhagen, Denmark).

STATISTICAL ANALYSES

All data were analysed by the following statistic software: Stat View PowerePC Version 5.0 (SAS Institute Inc, Cary, NC, USA), SPSS (version 17.0 or 18.0), SigmaStat (version 2.03) for Windows software (SPSS Inc., Chicago, IL), or R-program (version 3.0.0) nlme package.

Parametric variables are reported as the mean with standard deviation (SD) or standard error of the mean (SEM) or 95% confidence interval. Skewed data are shown as medians with range. Kolmogorov-Smirnov was used for testing normality. Differences between groups were evaluated by ANOVA or Chi-square (Study I), the Mann-Whitney U-Test (Studies II, III, V), linear mixed model (Study III) or ANOVA for repeated measures with the Tukey-Kramer post hoc test (Study IV). Differences within groups were tested by the Wilcoxon Signed Rank test (Studies II, III, V) with the post hoc Bonferroni correction, ANOVA on ranks and linear mixed model (Study III), or student´s t-test (Study IV). $P<0.05$ was considered statistically significant.

To estimate required sample sizes, power analysis was performed during study planning. Studies II and III were designed to discover a threefold difference in required volume of study fluid between groups, limiting the risk for Type I error to less than 0.05, while keeping the risk for a Type II error at less than 0.2. On the basis of our previous study, the number of subjects per group is also sufficient to detect a difference of 15% in MCF of the thromboelastometry.[123] In Study IV, 12 volunteers were considered necessary to detect a 15% difference in MCF between the groups, and in Study V, the number of volunteers required to discover a difference greater than 1 SD in MCF was 8, with an α- and ß- error of 0.05 and 0.2 respectively for these studies.

RESULTS

All patients and volunteers initially included completed the study, but for one patient in each group in Study II, the fluid management protocol was violated, and the data of these two patients were not analysed. In both Studies II and III, one of the patients in the RAC group required a mannitol bolus because of inadequate brain relaxation. The data of these two patients were analysed until the administration of mannitol, applying the intention-to-treat principle. All haemodilutions in Studies IV and V were successful. Of all the thromboelastometry tracings, 1.1% were technically unsuccessful and excluded from analysis.

HAEMODYNAMIC PROFILE

After patient placement in the sitting position, median systolic arterial pressure (SAP) decreased 8 (-95 to + 50) mmHg (Study I). Positioning was accompanied by a more than 20% decrease in SAP in 38% (Study I) and 25% (Study II) of the patients, whereas SAP was stable during surgery (See Study I, Fig 3, p.509). Of all patients, 69% (Study I) and 82% (Study II) received vasoactive drugs. In Study II, heart rate (HR) and MAP did not differ between groups during positioning or in the sitting position. CI and SVI increased during surgery in the HES group ($P<0.05$) but not in the RAC group (NS) (See Study II, Figure 2, p.734). No significant differences occurred between the groups regarding the total amount of vasoactive drugs used, neither for phenylephrine ($P=0.729$) nor for ephedrine ($P=0.317$). Doses of the continuous infusion of propofol ($P>0.05$), as well as the total dose of propofol ($P=0.581$), were comparable between groups. No difference in the total dose of fentanyl ($P=0.307$), remifentanil boluses ($P=0.926$), remifentanil infusion ($P=0.748$), or amount of local anaesthetics ($P=0.405$) emerged between groups.

In the prone position (Study III), neither HR or SVI differed between the groups during the entire study period; CI and MAP increased in the HES group ($P<0.05$), however, but not in the RAC group (NS) (See Study III, Figure 2, p.16). No significant differences emerged between groups as to total amount of vasoactives, neither for phenylephrine ($P=0.755$) nor for ephedrine ($P=0.239$). End-tidal concentrations of inhaled sevoflurane were comparable between groups ($P>0.05$), and doses of the continuous infusion of propofol ($P=0.768$), as well as the total dose of propofol ($P=0.725$) were comparable between groups, with no difference between groups in total dose of fentanyl ($P=0.653$), remifentanil ($P=0.195$), or the amount of local anaesthetics ($P=0.348$).

INCIDENCE OF VAE

VAE was observable in 19% (Study I) and 50% (Study II) of the patients operated on in the sitting position. In Study I, five patients had a greater than 0.7 kPa decrease in $ETCO_2$ as the only indication of VAE, resulting in a 26% incidence of VAE in this retrospective study. Study II showed no difference in incidence of VAE between the RAC and HES groups (P=0.458). VAE was usually detected at the beginning of surgery. None of the patients needed to be repositioned during surgery. According to Study I findings, all VAE patients had normal peripheral oxygen saturation during the whole period of surgery, and the changes in SAP were comparable to those of the no-VAE group. One patient with VAE developed bilateral infiltrates in the postoperative chest x-ray, but these changes disappeared on the first postoperative day. Neither duration of ventilator treatment nor hospital stay differed between the VAE- and no-VAE groups in Study I. All clinical or radiological signs of complications referable to systemic arterial air embolism were absent.

VOLUMES OF FLUIDS

Compared to HES, the mean cumulative dose of RAC needed to optimize fluid filling at 30 min after the sitting positioning was significantly higher (P<0.05), and the intraoperative fluid balance was more positive in the RAC than in the HES group (P=0.044, 95% CI -978 to -14) (Table 3). Comparable haemodynamics were achieved with the mean (SD) cumulative doses of HES or RAC 271 (47 mL) or 264 (50 mL) (P=0.699) before the sitting position, 343 (94) or 450 (156) (P=0.036) at 30 min after the positioning, and 464 (284) or 707 (425) respectively (P=0.087) at the end of surgery.

Compared to HES, the mean cumulative dose of RAC needed to optimize fluid filling at 30 min after the prone positioning was significantly higher (P<0.05). Comparable haemodynamics were achieved with the mean (SD) cumulative doses of HES or RAC 240 (51 mL) or 267 (62 mL) (p=0.207) before the prone position, 340 (124) or 453 (160) (p=0.039) 30 min after the positioning, and 440 (229) or 653 (368) respectively (p=0.067) at the end of surgery. No difference appeared in intraoperative fluid balance (P=0.110).

Table 3 Intra-operative fluid balance in Studies II and III.

	HES (II)	RAC(II)	HES (III)	RAC (III)
Pre Dose (mL)	271 ± 47	264 ± 50	240 ± 51	267 ±62
30 min Dose (mL)	343 ± 94 *	450 ± 156 *	340 ± 124 *	453 ± 160 *
End Dose (mL)	464 ± 284	707 ± 425	440 ± 229	653 ± 368
Total basal RAC Dose (mL)	750 ± 202	767 ± 240	813 ± 235	868 ± 354
Intraoperative blood loss (mL)	106 ± 106	136 ± 145	216 ± 160	201 ± 278
Intraoperative urine output (mL)	754 ± 671	488 ± 276	352 ± 262	407 ± 480
Intraoperative fluid balance (mL)	612 ± 650 *	1108 ± 520 *	799 ± 305	1074 ±569

Cumulative amounts of study fluids administered before the position (Pre), 30 min thereafter (30 min), and at the end of surgery (End). Values are mean ± SD.
*P<0.05 between groups
HES= hydroxyethylstarch 130/0.4, RAC= Ringer´s acetate

THROMBOELASTOMETRY FINDINGS

In Study II, thromboelastometry data were comparable between the groups (Table 4), and no difference emerged in blood loss between groups (*P*=0.536). Study III revealed a difference in FibTEM α-angle between the groups, although the clinical relevance of this finding is unclear. The formation and maximum strength of the fibrin clot were lower in the HES group, unlike in the RAC group (Table 4). In FibTEM analyses, α-angle (*P*=0.037) and MCF (*P*=0.012) decreased at the end of surgery in comparison with the baseline in the HES group, but in the RAC group these characteristics remained unchanged. In Study III, only one patient in the HES group needed transfusion of packed red blood cells during surgery, and intraoperative blood loss was comparable between groups (*P*=0.861).

Table 4 ROTEM® results before (Pre), and after boluses of study fluid (Post), and at the end of surgery (End) in Studies II and III.

	HES (II)	HES (III)	RAC (II)	RAC (III)
InTEM® MCF (mm)				
Pre	65.0 (49-78)	65.0 (57-70)	62.5 (49-74)	65.0 (58-76)
Post	65.5 (46-81)	65.0 (54-74)	65.0 (56-73)	64.0 (56-76)
End	64.0 (40-78)	65.0 (56-71)	63.0 (53-74)	67.0 (58-76)
InTEM® α-angle (º)				
Pre	75.5 (61-83)	77.0 (71-80)	76.5 (66-80)	76.5 (73-82)
Post	76.5 (61-85)	76.5 (72-78)	76.0 (70-80)	78.0 (73-83)
End	76.0 (38-83)	76.0 (72-79)	76.5 (65-82)	77.0 (73-82)
ExTEM® MCF (mm)				
Pre	65.5 (50-84)	61.0 (54-72)	60.0 (52-73)	62.5 (54-74)
Post	65.0 (38-80)	60.5 (52-70)	60.0 (55-73)	61.0 (54-75)
End	65.0 (44-78)	61.0 (53-73)	60.0 (55-69)	64.0 (57-76)
ExTEM® α-angle (º)				
Pre	74.5 (54-81)	75.0 (66-80)	75.0 (63-77)	73.5 (69-80)
Post	75.0 (45-84)	72.0 (63-78) #	75.0 (68-81)	74.0 (67-81)
End	73.0 (52-83)	73.0 (62-80)	74.0 (66-77)	75.0 (68-81)
FibTEM® MCF (mm)				
Pre	19.0 (6-39)	15.0 (11-25)	17.0 (11-26)	16.0 (9-28)
Post	17.0 (5-45)	14.5 (10-35)	17.0 (12-28)	15.5 (11-40)
End	17.0 (5-41)	13.0 (9-23) #	17.0 (9-32)	16.0 (10-31)
FibTEM® α-angle (º)				
Pre	75.0 (74-81)	70.0 (52-80)	74.0 (60-80)	68.5 (52-82)
Post	72.0 (61-84)	65.5 (59-81)	71.0 (60-81)	74.0 (51-82)
End	72.0 (57-81)	61.0 (32-77) # *	69.0 (58-80)	73.0 (55-84)
ApTEM® MCF (mm)				
Pre	69.0 (40-80)	62.0 (54-71)	63.0 (39-78)	65.0 (56-76)
Post	58.0 (52-81)	60.0 (54-78)	62.0 (17-78)	62.0 (54-75)
End	69.0 (49-83)	66.0 (55-72)	63.0 (59-78)	64.0 (57-78)
ApTEM® α-angle (º)				
Pre	76.0 (52-80)	76.0 (70-78)	73.5 (54-82)	75.0 (69-80)
Post	74.0 (64-82)	73.0 (69-80) #	75.0 (59-81)	74.0 (64-78)
End	74.0 (62-84)	74.0 (61-79)	74.0 (68-81)	75.0 (70-82)

Values presented as median (range).
# $P<0.05$ in comparison with Pre within the group (Wilcoxon Signed Rank Test).
* $P<0.05$ HES in comparison with RAC (ANOVA)
HES= hydroxyethylstarch 130/0.4, MCF= maximum clot firmness, RAC= Ringer´s acetate

The totally balanced fluid concept with a combination of balanced colloid and balanced crystalloid solutions has negative effects on whole blood coagulation comparable to those of combination of the respective unbalanced solutions in vitro (See Study IV, Figures 1-4, p.424-5). In EXTEM analyses, CT and CFT were prolonged in all 20- and 40 vol% dilutions with both balanced and unbalanced HES solutions compared to the control ($P<0.05$). In contrast, CT remained unchanged in the gelatin-diluted samples after 20 vol% haemodilution. MCF decreased in all the samples in comparison to the control after 20- and 40 vol% haemodilution in both EXTEM and FIBTEM analyses.

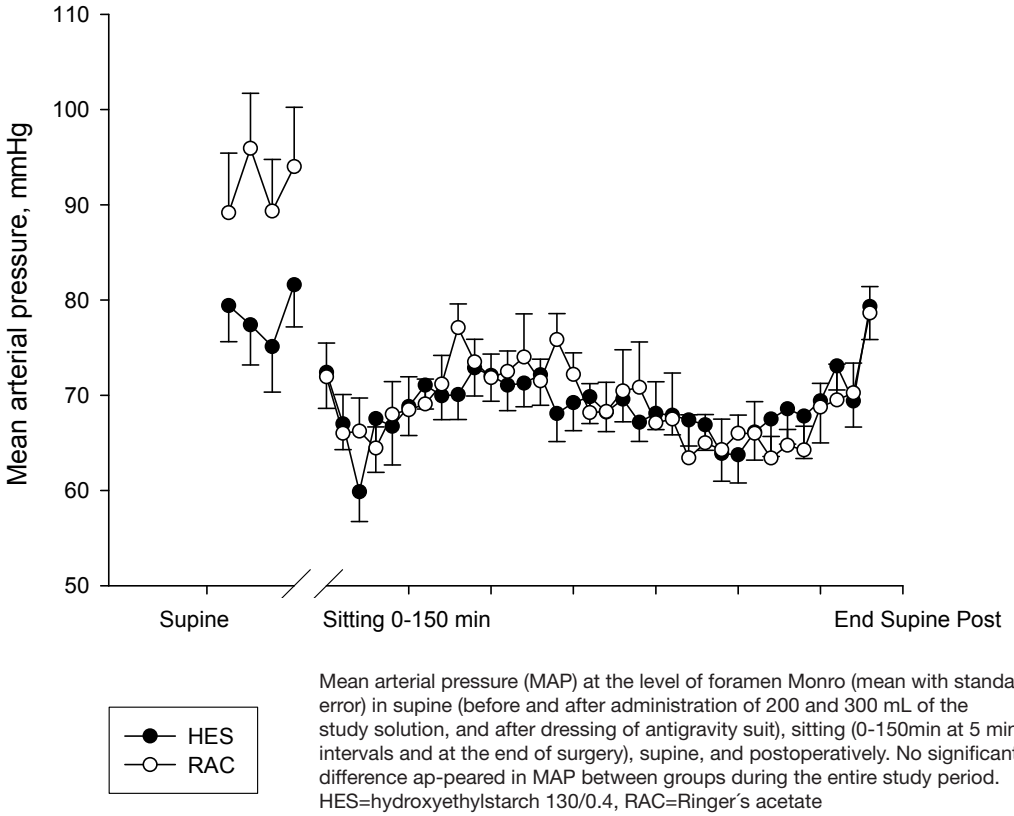
As measured by thromboelastometry, mannitol impaired whole blood coagulation. This impairment associated with mannitol was evident because of the delayed initiation of coagulation and fibrin formation (prolonged CFT), and decreased MCF in vitro. This effect was more pronounced with a greater degree of dilution and more pronounced for mannitol in combination with HES (See Study V, Tables 3 and 4, p.18). Because samples with similar mannitol concentration were compared, MCF decreased more in 20 vol% mannitol with HES than in 10 vol% mannitol in both EXTEM and FIBTEM analyses ($P<0.05$). No significant difference appeared in MCF between 20 vol% mannitol with RAC and 10 vol% mannitol.

DISCUSSION

SITTING POSITION AND HAEMODYNAMICS

The sitting position was associated with risk for hypotension in Studies I and II (38% and 25% of patients), especially during the positioning period. Depending on definition, the incidence of hypotension in association with the sitting position has ranged from 5 to 32%.[4] Our results are in accordance with these findings. GDT-administered fluid therapy with crystalloid or colloid before positioning in Study II did not prevent the hypotension induced by positioning (Figure 5), but provided stable haemodynamic values during the sitting position (See Study II, Figure 2, p.734). Despite fluid loading with 7 mL/kg crystalloid (Eufusol®) or 7 mL/kg colloid (Gelafundin®) before the sitting position, Buhre and coworkers found a 24% decrease in CI. In our study, CI remained stable with 9 mL/kg crystalloid (Ringer´s acetate); with 6 mL/kg colloid (Voluven®) CI even increased.

Figure 5.



Mean arterial pressure (MAP) at the level of foramen Monro (mean with standard error) in supine (before and after administration of 200 and 300 mL of the study solution, and after dressing of antigravity suit), sitting (0-150min at 5 min intervals and at the end of surgery), supine, and postoperatively. No significant difference ap-peared in MAP between groups during the entire study period. HES=hydroxyethylstarch 130/0.4, RAC=Ringer´s acetate

SITTING POSITION AND VAE

The sitting position was associated with risk for VAE in Studies I and II (26 and 50%) especially during the beginning of surgery. These findings are in line with previous ones, in which the incidence of VAE diagnosed by precordial Doppler has been 25 to 50% of patients undergoing craniotomy in the sitting position.[4] In Study II, VAE was diagnosed by precordial Doppler or by a 0.3-kPa or greater decrease in $ETCO_2$. The magnitude of $ETCO_2$ change indicating VAE ranges from 0.3 to 0.7 in the literature,[124, 125] but for a prospective study the chosen value was considered appropriate. The incidence of VAE reported in Study I may have been underestimated due to the retrospective study design and the higher cut-off value for $ETCO_2$ (>0.7kPa).

GDT WITH CRYSTALLOID OR COLLOID AND FLUID BALANCE

A crystalloid vs. colloid volume ratio of 1.0 before positioning and 1.5 at the end of surgery is lower than expected (Studies II, III). It is commonly believed that 2 to 3 times more crystalloid than colloid fluid is necessary to restore and maintain filling pressures in the treatment of hypovolemia.[100] Recent studies have shown, however, that the volume ratio between crystalloid and colloid in the critically ill is in fact more in the range of 1 to 2.[101] Our results are in accordance with these findings.

In Study II, the intraoperative fluid balance was more positive in the RAC than in the HES group, whereas in Study III, the intraoperative fluid balance was comparable between groups. In Study II, two patients (both in the RAC group) were classified as non-responders, and volume expansion was halted, whereas four patients (3 in the RAC group and 1 in the HES group) in Study III were classified as non-responders. A patient was considered a non-responder if the SV did not increase with three consecutive boluses of study fluid during surgery; in such cases, the volume expansion was halted. Without these limits for non-responders, the difference in fluid balance between the groups might have been more distinct.

With GDT-administered crystalloid or colloid for patients undergoing neurosurgery in the sitting and prone position, the amount of RAC was 25 to 34% higher than the amount of HES to achieve a stable haemodynamic profile. However, most patients undergoing neurosurgery in the sitting and prone positions can be managed with

an acceptable volume of RAC instead of HES; the latter may cause a blood coagulation disturbance even at relatively low doses. Recently, administration of HES solutions in surgical patients has been questioned due to the possibly increased risk for renal insufficiency. No evidence exists as to the mechanism for renal insufficiency developing after colloid resuscitation, and the pathogenesis of acute renal failure in septic patients with low renal perfusion pressure in combination with capillary leakage differs.

GDT WITH CRYSTALLOID OR COLLOID AND POSITIONING

Studies II and III demonstrated that GDT-administered crystalloid is as effective as GDT-administered colloid in maintaining stable arterial blood pressure during neurosurgery in the sitting and the prone position, but the effect on CI was more favourable in the HES group in both of these positions. Colloid fluid loading in surgical patients has earlier been shown to lead to a greater cardiac response than with saline.[100] The positive effect of GDT-administered colloid on CI may justify administration of HES according to the goal-directed principle in hypovolemic patients requiring instant restoration of haemodynamics without excessive fluid load.

In our studies, the volume of fluid (colloid/crystalloid) needed before positioning (Study II: 271/264 mL, Study III: 240/267 mL) was surprisingly low. Our studies also show that with GDT-administration of fluids, the prone and sitting positionings reduce CI neither in the HES nor in the RAC group. In a study by Biais and coworkers, a bolus of 500 mL of 6% hetastarch before the prone positioning did not significantly prevent a decrease in CO in the prone position.[126] Differences in study protocols, such as maintenance of anaesthesia, use of vasopressors, haemodynamic endpoints, fluid bolus volume, and time intervals for haemodynamic measurements, may explain the differences in CO response. In spinal surgery patients, the reduction in CO on turning patients prone was greater during maintenance of anaesthesia with propofol than with inhalation anaesthesia.[127] Biais´s study had set measurements at a few predefined time intervals, but in Studies II and III, the haemodynamic measurements were performed throughout surgery at intervals of 5 minutes. Differences in positioning system with varying pressure on the inferior vena cava also affect the degree of haemodynamic changes in the prone position.[128]

Haemodynamic response to fluid administration is largely dependent on the combined effect of the degree of hypovolemia, dosing regimen, and type of fluid. Patients in this study had a short fasting period preoperatively,

and their intra-operative blood loss was minimal. According to a study by Bundgaard-Nielsen and coworkers on GDT guided by oesophageal Doppler, 70% of patients had a functional intravascular volume deficit before surgery, and the median amount of colloid required to establish a maximal SV was 200 mL (range 200-600 mL).[129, 129] The volume of fluid required (200-300 mL of HES or 200-400 mL RAC) in our studies (II and III) is in accordance with these findings, but for the Bundgaard-Nielsen group, 15% of the patients had a clinically relevant volume deficit of ≥ 400mL. The fasting rules were the same, but their study included abdominal surgery patients, and they applied positive pressure ventilation which affects intravascular volume. In our study, the initial bolus of fluid was 200 mL, but further boluses were 100 mL in volume, increasing the sensitivity for reaching the threshold of optimal fluid filling.

GDT WITH CRYSTALLOID OR COLLOID AND EFFECTS ON COAGULATION

For RAC we found no effect on coagulation measured with thromboelastometry, but the effect of HES on coagulation measured with thromboelastometry varied among the studies. In Study III, the formation and maximum strength of the fibrin clot were decreased after an average dose of 440 mL of HES 130/0.4, whereas in Study II, an average dose of 460 mL of HES 130/0.4 did not impair the coagulation profile in thromboelastometry. The clinical relevance of these findings remains unclear. Intraoperative blood loss in these patients was very low and did not differ between the groups in either study. In neurosurgical patients, however, even minimal bleeding can have serious consequences. The volumes of fluids distributed were small; therefore the effect on haemostasis was minimal, and we observed no crystalloid-induced hypercoagulability.

Study II involved craniotomy patients alone, whereas patients in Study III were mainly undergoing spinal surgery. An earlier study in neurosurgical patients showed increased coagulability by TEG® during surgery; these changes were more pronounced in patients undergoing craniotomy than in those undergoing spinal procedures.[119] Heesen and coworkers showed that thromboplastin is released during intracranial surgery, a release that may contribute to the hypercoagulability.[120] Differences in the effect of HES on coagulation, measured with thromboelastometry, between Studies II and III may in part be due to differences in type of surgery. Posture should also be considered a significant factor affecting coagulation; the sitting position is associated with increased viscosity in the lower limbs which could contribute to activation of the coagulation

system.[130] Furthermore; VAE has been associated with a decrease in platelet count, and in vitro studies have shown that air-blood contact leads both to complement and to platelet activation.[131]

GDT WITH CRYSTALLOID OR COLLOID AND OSMOLARITY

Because RAC (270 mOsm/l) is slightly hypo-osmolaric in relation to plasma (295 mOsm/l), additional sodium was added to the basal infusion of RAC for the craniotomy patients in Study II. HES 130/0.4 is dissolved in normal saline (308 mOsm/l) and should not lower serum osmolality. In Study II, one patient in the RAC group needed a mannitol bolus, and two patients in the HES group were administered a bolus of hypertonic saline for treatment of brain swelling. In Study II, the neurosurgeon reported one case of difficulty with closing the wound of a patient in the RAC group due to clinically observed brain oedema. Otherwise no obvious brain swelling occured. Serum osmolarity was not measured.

BALANCED FLUIDS AND EFFECT ON COAGULATION

In Study IV, a totally balanced fluid concept offered no advantages regarding whole blood coagulation in vitro, as measured by thromboelastometry. Later, an ex vivo study by Schaden and coworkers confirmed this thromboelastometry finding in healthy volunteers and also concluded that the carrier solution of HES had a minimal effect on platelet aggregation.[112] Further clinical studies are required to verify this finding in patients.

MANNITOL AND EFFECT ON COAGULATION

Although mannitol is commonly administered to neurosurgical patients to reduce ICP and improve surgical conditions during craniotomy, the possible effects of mannitol on blood coagulation have not been investigated. In Study V, mannitol alone and in combination with HES 130/0.4 impaired clot propagation and clot strength in vitro. This negative effect of mannitol on thromboelastometry tracings was later confirmed in another in vitro study by Luostarinen and coworkers,[132] who also reported that blood coagulation is disturbed more by mannitol than by equiosmolar hypertonic saline.[132] Further clinical studies are necessary to investigate any possible interference of mannitol in blood coagulation.

LIMITATIONS OF THE STUDIES

Study I is retrospective, and thus may be biased. Studies II and III are small clinical studies not designed to reach conclusions on the safety profiles of various fluids. Because of their small populations, the studies did not aim to detect differences in clinical outcome. The anaesthesiologists were not blinded to treatment group, but the fluid administration was guided by specific protocols. In Study III, the anaesthesia was not totally standardized. Studies IV and V are in vitro studies, so in vivo conditions, results should be applied cautiously. The in vitro model does not include the endothelial effects on coagulation, or the pharmacokinetics and metabolism of the solutions.

METHODOLOGICAL CONSIDERATIONS

In Studies II and III, haemodynamic variables including CO were measured by the Vigileo-FloTrac system (version 3.02). Earlier studies measuring CO with the first and second version of the Vigileo-FloTrac system showed poor agreement in low systemic vascular resistance states such as during high-dose vasopressor therapy.[36, 133] Compared to previous versions, the new third-generation system has improved.[134] Acute changes in peripheral vascular resistance may, however, reduce reliability in measuring CO accurately.[135] We included only elective neurosurgical patients, and the doses of vasopressor therapy were low; the risk of altered vascular resistance state should thus be minimal. No difference in vasopressor therapy doses between groups occurred. Because haemodynamic measurements may be influenced by differences in body surface area formulas in morbidly obese patients,[136] we excluded such patients.

In Studies II to V, modified thromboelastometry coagulation analysis (ROTEM®) was performed. Age, gender, and oral contraception may influence the parameters determined by ROTEM®.[118] In our studies, no patient was on oral contraception, and age distributions between groups were comparable. Distribution by gender differed between groups only in Study V.

CONCLUSIONS

The aim of the study was to examine the effects and possible side-effects of fluid therapy that comprised goal-directed therapy with a crystalloid or a colloid in patients undergoing neurosurgery in the sitting and prone positions. The results showed that most of the patients undergoing neurosurgery in the sitting and prone position could be managed with an acceptable volume of RAC.

The sitting position is associated with risk for hypotension and for VAE despite fluid filling. GDT with either RAC or HES solutions in combination with vasoactives maintains a stable haemodynamic state during neurosurgery in the sitting and prone position. During neurosurgery, HES 130/0.4 had a slightly greater positive effect on the haemodynamic parameters than did RAC. In hypovolemic patients requiring instant restoration of haemodynamics without excessive fluid load, administration of HES according to the goal-directed principle might be justified.

The effect of HES 130/0.4 on coagulation as measured by thromboelastometry indicates the possible decreased formation and maximum strength of the fibrin clot. The clinical effect of HES 130/0.4 on coagulation is still unclear. Taking into account any safety concerns with regard to coagulopathy, renal failure, and mortality associated with HES solutions in other patient groups, any use of HES 130/0.4 in neurosurgical patients should be cautious.

Based on in vitro observations, a totally balanced fluid concept does not offer advantages in regard to haemostatic mechanisms. Mannitol induces a whole-blood coagulation disorder in vitro, especially in combination with HES 130/0.4. The combination of mannitol and HES solutions should be avoided in neurosurgery, especially in any case of a disturbance in haemostasis.

CLINICAL IMPLICATIONS

The sitting position in neurosurgery is associated with risks such as haemodynamic instability and VAE. With careful titration of fluid therapy in combination with vasoactives, the haemodynamic changes induced by positioning can be minimized. Early recognition of air leakage by careful monitoring and good co-operation between the surgical and anaesthesia teams is important in reducing the risk for VAE-related complications. The advantages with this position are considerable for craniotomy patients with lesions in the pineal or cerebellopontine regions, and the risks can be reduced by an experienced team.

The volume ratio between crystalloid and colloid in these studies was surprisingly low. With SV-directed administration of fluids, most patients undergoing neurosurgery in the sitting and prone position can be managed with acceptable volumes of RAC, avoiding the possible negative effects on coagulation of HES 130/0.4.

The totally balanced fluid concept offers no advantages regarding coagulation mechanisms, but the administration of buffered fluids is associated with less metabolic interference such as by metabolic acidosis and hyperchloraemia. The combination of mannitol and HES solutions should be avoided, at least until the coagulation effects are further investigated in neurosurgical patients.

IMPLICATIONS FOR FUTURE STUDIES

Despite the increasing research efforts of the past years, many issues concerning perioperative fluid therapy remain. This thesis attempted to answer some questions about fluid therapy in neurosurgical patients, but further questions remain. The effect of fluid therapy on clinical outcome should undergo further evaluation.

The volumes of fluid needed in this study were relatively low. The effects of fluid therapy on plasma colloid oncotic pressure and the possible effect on cerebral oedema formation require further study in patients. Based on experimental studies, a decrease in plasma colloid oncotic pressure, in addition to decreased plasma osmotic pressure, may aggravate cerebral oedema.

The possible negative effects of mannitol on coagulation indicated by in vitro studies require further studies in neurosurgical patients.

The monitoring of fluid therapy during neurosurgery should be developed for tissue perfusion monitoring to minimize risk of inadequate cerebral blood flow perioperatively.

This study included elective neurosurgical patients. Fluid therapy in subgroups such as traumatic brain-injury and SAH patients requires further study.

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